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Original Article

Influence of Third-generation Cephalosporin Resistance on Adult In-hospital Mortality From Post-neurosurgical Bacterial Meningitis

Chia-Jung Chang, Jung-Jr Ye, Chien-Chang Yang, Po-Yen Huang, Ping-Cherng Chiang, Ming-Hsun Lee*

Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan.

BACKGROUND/PURPOSE: To investigate the clinical features, etiology and predictors of in-hospital mortality in adults with post-neurosurgical bacterial meningitis.

METHODS: This retrospective analysis included 60 adult patients with culture-proven post-neurosurgical bacterial meningitis hospitalized between September 2006 and August 2008.

RESULTS: Of the 60 patients, 88.3% had monomicrobial infection and 11.7% had mixed infection. The mean duration from the first neurosurgical procedure to the diagnosis of meningitis was 21 days (range, 1–134 days). The median frequency of neurosurgical procedure before meningitis was 1 (range, 1–5). A total of 69 isolates were identified from the cerebrospinal fluid, the most common pathogens were Gram-negative bacilli (43, 62.3%), followed by Gram-positive bacteria (24, 34.8%). The three most common Gram-negative bacilli were *Serratia marcescens* (7, 10.1%), *Klebsiella pneumoniae* (6, 8.7%), and *Enterobacter cloacae* (4, 5.8%). *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates comprised less than 3%. Notably, glucose non-fermenting Gram-negative bacilli other than *Acinetobacter* and *Pseudomonas* spp. accounted for 11.6% of the total. Of the Gram-negative bacilli, resistance rates to the third-generation cephalosporins, ceftriaxone and ceftazidime, were 58.1% and 34.9%, respectively. The two most common Gram-positive pathogens were *Staphylococcus aureus* (10, 14.5%) and coagulase-negative staphylococci (including *S. epidermidis*) (10, 14.5%). The in-hospital mortality rate was 15.0%, which was significantly related to Gram-negative bacilli resistant to third-generation cephalosporins in multivariate analysis (adjusted odds ratio = 33.65; $p = 0.047$).

CONCLUSION: These findings may portend the spread of serious resistance to third-generation cephalosporins in nosocomial Gram-negative bacilli throughout the neurosurgical units, suggestive of the need to reassess the empirical use of third-generation cephalosporins in post-neurosurgical bacterial meningitis.

KEYWORDS: bacterial meningitis, Gram-negative bacilli, post-neurosurgical

*Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, 5 Fu-Shin Street, Gueishan 333, Taoyuan, Taiwan.

E-mail: drharrylee@gmail.com

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Introduction

Post-neurosurgical bacterial meningitis is not common and there is little published in the literature in English. The exact incidence of meningitis after neurosurgical procedures is variable and is yet unknown, but the reported incidence varies from 0.3% to 0.8%.[1] Post-neurosurgical meningitis is a potentially life-threatening infection of the central nervous system (CNS) and is associated with worsening of neurological outcome and increased mortality.[2] It has become an important subgroup of bacterial meningitis within the hospital setting. Surgical procedures most commonly related to bacterial meningitis include craniotomy for head injury, brain tumor or intracranial hemorrhage, external ventricular device placement, ventriculoperitoneal shunt implantation and ventriculostomy.[3] The diagnosis of bacterial meningitis following neurosurgery is often difficult due to a lack of specificity regarding the relevant clinical features and laboratory findings.

The prevalence rates for pathogens causing bacterial meningitis vary with time, geographical distribution, age, underlying medical and/or surgical conditions, and mode of infection.[4–6] The epidemiologic changes in bacterial meningitis may alter clinicians' behavior regarding antibiotic prescription.[7,8] Antimicrobial therapy for post-neurosurgical meningitis is complicated by the emergence of multi-antibiotic resistant strains in recent years. This trend and poor penetration of some antimicrobial agents into the cerebrospinal fluid (CSF) impose limitations on antimicrobial selection.

Potential consequences from the increasing frequency of neurosurgical procedures and the widespread use of empirical vancomycin and antipseudomonal β-lactam antibiotics, particularly third-generation cephalosporins, for post-neurosurgical infections[7] may have led to the change in the hospital epidemiology and clinical spectrum of post-neurosurgical meningitis seen in recent years.[9] Thus we conducted a 2-year retrospective analysis of consecutive episodes of post-neurosurgical bacterial meningitis among a predominantly adult population to investigate the etiology, clinical characteristics, laboratory, microbiology and antimicrobial therapy of post-neurosurgical bacterial meningitis, and analyzed their impact on in-hospital mortality.

Methods

Patients and study design

Adult patients (age ≥ 16 years) with a diagnosis of bacterial meningitis after a neurosurgical procedure and with relevant CSF cultures positive for one or more bacterial organisms between September 2006 and August 2008 were retrospectively identified through the computer database of discharge diagnosis in the Clinical Microbiology department at Chang Gung Memorial Hospital–Linkou Medical Center, a 3,300-bed university hospital and tertiary referral center in northern Taiwan, providing 260 ordinary neurosurgical beds and 32 intensive-care-unit beds. Patients having partial treatment at other hospitals and subsequently transferred to the Clinical Microbiology Department at Chang Gung Memorial Hospital–Linkou Medical Center were excluded. Patients with evidence of concomitant chronic meningitis or encephalitis not due to bacterial pathogens were also excluded.

Data collected from the enrolled patients included demographic characteristics, comorbid illness, conditions for neurosurgery, clinical features, laboratory data, bacteriology, antimicrobial susceptibility testing, treatment modalities and clinical outcomes. Comorbid illnesses included hepatic dysfunction with a serum bilirubin level ≥ 2.0 mg/dL or liver cirrhosis, renal insufficiency with a serum creatinine level ≥ 2.0 mg/dL or a requirement for hemodialysis, chronic pulmonary disease, cardiac disease, diabetes mellitus, and hematological or solid organ malignancies. Patient outcomes were classified into "survival" and "deceased" (in-hospital mortality) groups to elucidate the contributing factors.

Definitions

The diagnostic criteria for a definite bacterial meningitis included micro-organisms being isolated in one or more CSF cultures and at least one of the following: (1) clinical features consistent with meningitis, including fever, consciousness disturbance, seizure, or signs of meningeal irritation; and (2) consistent CSF findings, a decreased glucose concentration (CSF/serum glucose ratio < 0.3 or CSF glucose < 50 mg/dL if serum glucose was not available), increased lactate (> 18.9 mg/dL) and protein concentrations (> 32 mg/dL), and pleocytosis (≥ 10 white blood cells/uL) with a predominance of polymorphonuclear

cells.[4,6] "Post-neurosurgical" meningitis was defined as meningitis developed within 3 months of a neurosurgical procedure. "Recurrence" of meningitis was defined as two or more episodes caused by a different bacterial pathogen, or a second or further episode due to the same organism with a more than 3-week interval after the completion of therapy for the initial episode. "Relapse" of meningitis was considered if it was caused by the same organism within 3 weeks of the completion of therapy for the initial episode.[4] Consecutive cultures growing the same bacterial organism, or consecutive cultures within 7 days growing different pathogens, were regarded as the same episode.

Mixed bacterial meningitis was defined as two or more bacterial organisms isolated from the initial CSF culture.[10] Contamination was defined as growth of bacterial pathogen from the CSF in a patient without clinical features of meningitis and consistent CSF findings. "Bacteremia" was defined as the isolation of bacterial pathogens in more than one set of blood cultures. Fever was defined as an ear temperature ≥ 38 °C. Shock was defined as systolic blood pressure ≤ 90 mmHg measured on the same day as the collection of blood cultures and was unrelated to other possible causes of shock, e.g. hypovolemic and cardiogenic shock. Respiratory failure was defined as the need for endotracheal intubation with mechanical ventilator support. Third-generation cephalosporin-resistant Gram-negative bacilli (GNB) refer to GNB resistant to at least one antibiotic (either ceftriaxone or ceftazidime). Appropriate antimicrobial therapy was defined as the administration of antimicrobial agents that were effective *in vitro* according to drug susceptibility testing and were capable of passing through the blood-brain barrier to achieve potentially therapeutic levels.

Microbiology

The antimicrobial susceptibility testing of each isolate was performed using the disk diffusion method according to Clinical and Laboratory Standards Institute criteria.[12]

Statistical analysis

All statistical analyses were done using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Tests performed in univariate analysis were χ^2 or Fisher's exact test for categorical variables and Student's *t* test for continuous variables, as appropriate. Odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of any association as well as the precision of the estimate of effect in the outcome analysis. All variables with a *p* value of < 0.1 in univariate analysis and variables of interest (e.g. third-generation cephalosporin-resistant or -sensitive GNB) were included in a logistic regression model for multivariate analysis. All tests were two-tailed, and a *p* value of < 0.05 was considered significant.

Results

During the 2-year study period, 704 adult patients had a diagnosis of bacterial meningitis and a total of 71 episodes in 60 patients with culture-proven bacterial meningitis after neurosurgical procedures were included. Patients' demographics, associated neurosurgical conditions, clinical features and laboratory data are summarized in Table 1. Of the 60 patients, 30 were men and 30 were women, with a mean age of 56 years (range, 16–82 years), representing a population of seniority. Fifty-three patients had a single episode of post-neurosurgical meningitis. Seven patients who had more than one episode were included in the category of "recurrent meningitis".

The conditions for performing neurosurgical procedures included ischemic or hemorrhagic cerebrovascular accident (22; 36.7%), benign or malignant brain tumors (20; 33.3%), traumatic brain injury (9; 15.0%) and others (9; 15.0%). The mean duration from the first neurosurgical procedure to the diagnosis of meningitis was 21 days (range, 1–134 days). The median frequency of neurosurgical procedure before meningitis for all 60 patients was 1 (range, 1–5). Of the 60 patients, 30 (50.0%) had at least one comorbid illness. Diabetes mellitus was the most frequent (14, 23.3%), followed by malignancy (9, 15.0%) and renal insufficiency (7, 11.7%). Fever was the most common clinical manifestation (44, 73.3%), followed by respiratory failure (16, 26.7%) and altered consciousness (12, 20.0%). Fever and progressive deteriorating consciousness were two major clinical presentations, and about 18–26% of patients would progress to shock and respiratory failure. The initial mean Glasgow Coma Scale (GCS) score on presentation was 10 (range, 3–15).

The ranges of CSF routine and biochemistry data were as follows: glucose level = 0–206 mg/dL (56.7 ± 38.6 mg/dL); total protein = 10.9–5,200 mg/dL (371.4 ± 844.9 mg/dL);

Table 1. Demographic and clinical characteristics of 60 patients with post-neurosurgical bacterial meningitis

Characteristics	Value[a]
Demographic parameters	
Mean age (yr)	56±15
Sex, male:female	30:30
Episodes of neurosurgery before meningitis	1.0 (1–5)
Interval between meningitis and the initial neurosurgery (d)	21.0±24.9
Symptoms on presentation	
Fever	44 (73.3)
Headache	11 (18.3)
Neck stiffness	3 (5.0)
Seizure	5 (8.3)
Altered consciousness	12 (20.0)
Nausea or vomiting	7 (11.7)
Shock	11 (18.3)
Respiratory failure	16 (26.7)
Initial Glasgow Come Scales score on presentation	10±4
CSF data[b]	
Leukocyte count (/uL)	5,683.6±21,182.3
Neutrophil (%)	57.9±39.4
Glucose level (mg/dL)[c]	56.7±38.6
Protein level (mg/dL)	371.4±844.9
Lactate level (mg/dL)	76.2±80.1
Positive Gram stain result	47 (70.0)
Peripheral blood study[b]	
Serum leukocyte count (/uL)	13,370.1±5,415.5
Platelet count (/uL)	288,121.4±130,950.9
CRP (mg/L)	102.2±106.3
Bacteremia	8 (26.7)
Mortality	9 (15.0)

[a]Data presented as *n* (%), mean±standard deviation or median (range); [b]not every patient had every tests; [c]CSF sugar < 5 mg/dL was counted as 0. CSF=cerebrospinal fluid; CRP=C-reactive protein.

Table 2. The 69 cerebrospinal fluid isolates from 60 patients with post-neurosurgical meningitis

Organism[a]	*n* (%)
Gram-negative organisms	43 (62.3)
Enterobacteriaceae	28 (40.6)
Serratia marcescens	7 (10.1)
Klebsiella pneumoniae	6 (8.7)
Enterobacter cloacae	4 (5.8)
Klebsiella oxytoca	3 (4.3)
Escherichia coli	3 (4.3)
Morganella morganii	1 (1.4)
Proteus vulgaris	1 (1.4)
Enterobacter aerogenes	1 (1.4)
Escherichia hermannii	1 (1.4)
Citrobacter freundii	1 (2.3)
Glucose non-fermenting GNB	15 (21.7)
Acinetobacter spp.[b]	3 (4.3)
Acinetobacter baumannii	2 (2.9)
Pseudomonas aeruginosa	2 (2.9)
Sphingomonas paucimobilis	2 (2.9)
Stenotrophomonas maltophilia	1 (1.4)
Others	5 (7.2)
Gram-positive organisms	24 (34.8)
Staphylococcus aureus[c]	10 (14.5)
Coagulase-negative staphylococci[d]	10 (14.5)
Enterococcus faecalis	1 (1.4)
Enterococcus durans	1 (1.4)
β-*Streptococcus* Gr. D	1 (1.4)
Bacillus spp.	1 (1.4)
Anaerobes	2 (2.9)
Propionibacterium acnes	2 (2.9)

[a]Polymicrobial isolates were present in patient or one specimen; [b]*Acinetobacter baumannii* was not included; [c]two isolates were methicillin-sensitive and eight isolates were methicillin-resistant; [d]*Staphylococcus epidermidis* (*n*=3), *Staphylococcus capitis* (*n*=1), and other unidentified coagulase-negative Staphylococci (*n*=6). GNB=Gram-negative bacilli.

lactate=12.9–359 mg/dL (76.2±80.1 mg/dL); and white blood cell count=<5 to 149,375 cells/uL (5,683.6±21,182.3 μL). Blood cultures were performed in 30 patients, and eight were positive. The organisms grown from blood cultures were the same as those from the CSF specimens.

Among these 60 patients, 51 (85.0%) survived and nine (15.0%) died. Fifty-three (88.3%) had a monomicrobial infection and seven (11.7%) had a mixed infection. The causative pathogens isolated from the CSF are listed in Table 2. Of the total 69 identified isolates, 43 (62.3%) were Gram-negative organisms, 24 (34.8%) were Gram-positive organisms, and two (2.9%) were anaerobes. The leading GNB were *Enterobacteriaceae* (28, 40.6%) and glucose non-fermenting GNB (15, 21.7%). The Gram-positive bacteria were as follows: *Staphylococcus aureus* (10, 14.5%), coagulase-negative staphylococci (CoNS, including *S. epidermidis*) (10, 14.5%),

Table 3. Antimicrobial resistance of the causative organisms from the cerebrospinal fluid of 60 patients with post-neurosurgical meningitis[a]

Antimicrobial agent[b]	Gram-negative organisms					Gram-positive organisms
	Serratia marcescens (*n*=7)	*Klebsiella pneumoniae* (*n*=6)	*Enterobacter cloacae* (*n*=4)	Glucose non-fermenting GNB[c] (*n*=15)	Total (*n*=43)	
Ceftriaxone[d]	0 (0)	1 (16.7)	4 (100)	15 (100)	25 (58.1)	–
Ceftazidime	0 (0)	1 (16.7)	4 (100)	5 (33.3)	15 (34.9)	–
Cefepime	0 (0)	1 (16.7)	4 (100)	3 (20.0)	12 (27.9)	–
Carbapenems	0 (0)	0 (0)	0 (0)	5 (33.3)	5 (11.6)	–
Oxacillin	–	–	–	–	–	13 (65.0)[e]
Vancomycin	–	–	–	–	–	0 (0.0)[f]

[a]Data presented as *n* (%); [b]*Stenotrophomonas maltophilia* was viewed as intrinsic resistance to ceftazidime, ceftriaxone, cefepime and carbapenems;[27,28] [c]including *Acinetobacter* spp. (*n*=5), *Pseudomonas* spp. (*n*=2), *Sphingomonas paucimobilis* (*n*=2), *Stenotrophomonas maltophilia* (*n*=1), other unidentified glucose non-fermenting GNB (*n*=5); [d]glucose non-fermenting GNB were resistant to ceftriaxone; [e]susceptibility testing was available for 20 isolates; [f]susceptibility testing was available for 23 isolates. GNB=Gram-negative bacilli.

Enterococcus spp. (2, 2.9%), *Streptococcus* spp. (1, 1.4%), and *Bacillus* spp. (1, 1.4%).

The three most common GNB were *Serratia marcescens* (7, 10.1%), *Klebsiella pneumoniae* (6, 8.7%), and *Enterobacter cloacae* (4, 5.8%). *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates comprised less than 3%. Notably, glucose non-fermenting GNB other than *Acinetobacter* and *Pseudomonas* spp. accounted for 11.6% of the total isolates. *S. aureus* and CoNS (including *S. epidermidis*) were the two most common Gram-positive pathogens. The antimicrobial resistance of the causative organisms is listed in Table 3. Among the 43 GNB isolates on the initial positive CSF sampling, 25 (58.1%) were resistant to ceftriaxone, 15 (34.9%) were resistant to ceftazidime, and five (11.6%) were resistant to carbapenems. All four *E. cloacae* isolates were resistant to ceftriaxone and ceftazidime, and 5/15 glucose non-fermenting GNB isolates were resistant to ceftazidime. In comparison with the GNB isolates susceptible to third-generation cephalosporins, those isolates resistant to third-generation cephalosporins had the higher rate of third-generation cephalosporin exposure ≥72 hours within 2 weeks before the onset of meningitis, but there was no statistically significant difference between these two groups (32.0% *vs.* 11.1%; $p=0.153$). Of the 10 *S. aureus* isolates, eight (80%) were methicillin-resistant strains, and five (50%) implicated CoNS isolates were also methicillin-resistant. As disk testing is not reliable for vancomycin, the susceptibilities of the CoNS and *S. aureus* isolates to vancomycin remain unknown.

The analysis of potential risk factors for in-hospital mortality is listed in Table 4. Univariate analysis comparison between the surviving and deceased patients revealed the following significant factors: shock ($p=0.05$), respiratory failure ($p=0.001$), low GCS score at the onset of meningitis ($p=0.002$), and decreased platelet count ($p=0.019$). Variables used in multivariate analysis (Table 5) included shock, respiratory failure, initial GCS score, platelet count and GNB in CSF culture for module A. For modules B and C, we replaced the variable, "GNB", with "third-generation cephalosporin sensitive" and "third-generation cephalosporin resistant" GNB, respectively. After analysis of the aforementioned variables, the presence of third-generation cephalosporin resistant GNB in the CSF ($p=0.047$) was independently associated with in-hospital mortality for patients with post-neurosurgical meningitis.

Discussion

In this study, several findings are of interest. First, an obvious increase in GNB isolated from the CSF specimens of the patients with post-neurosurgical meningitis was noted. GNB were responsible for 62.3% of the total isolates. The ratio of GNB to Gram-positive pathogens was about 1.7:1,

Table 4. Univariate analysis of risk factors for in-hospital mortality in patients with post-neurosurgical meningitis

Variables	Survival[a] (n=51)	Deceased[a] (n=9)	OR (95% CI)	p
Demographic parameters				
Age (yr)	56±15	58±15	–	0.688
Sex, female	23 (45.1)	7 (77.8)	4.26 (0.09–0.81)	0.145
Conditions for neurosurgery				
CVA	19 (37.3)	3 (33.3)	0.84 (0.19–3.77)	1.000
Brain tumor	18 (35.3)	2 (22.2)	0.52 (0.10–2.79)	0.704
Traumatic brain injury	7 (13.7)	2 (22.2)	1.80 (0.31–10.46)	0.612
Others[b]	7 (13.7)	2 (22.2)	1.80 (0.31–10.46)	0.612
Interval between meningitis and the initial neurosurgery (d)	20±21	25±41	–	0.557
Comorbid illness[c]				
Hepatic dysfunction	2 (3.9)	1 (11.1)	3.06 (0.25–37.84)	0.391
Renal insufficiency	5 (9.8)	2 (22.2)	2.63 (0.43–16.27)	0.281
Diabetes mellitus	11 (21.6)	3 (33.3)	1.82 (0.39–8.47)	0.423
Malignancy	6 (11.8)	3 (33.3)	3.75 (0.74–19.08)	0.125
Symptoms on presentation[c]				
Shock	7 (13.7)	4 (44.4)	5.03 (1.08–23.40)	0.050
Respiratory failure	9 (17.6)	7 (77.8)	16.33 (2.90–91.99)	0.001
Initial GCS score on presentation	11.0±3.4	7.1±3.2	–	0.002
CSF data[c]				
Glucose level (mg/dL)	59.8±37.8	37.1±40.3		0.150
Peripheral blood study[c]				
Platelet count (/uL)	305,872±122,117	195,422±143,623		0.019
CRP (mg/L)	83.0±78.0	191.0±169.7		0.118
Neurosurgery-related				
Re-operation times after meningitis	1.3±1.9	1.2±1.0	–	0.890
Implanted CSF device[d]	41 (80.4)	7 (77.8)	0.85 (0.15–4.75)	1.000
Post-operation CSF leakage	10 (19.6)	2 (22.2)	1.17 (0.21–6.52)	1.000
Recurrence or relapse				
Recurrence	7 (13.7)	0 (0.0)	0.31 (0.02–5.95)	0.580
Relapse	3 (5.9)	0 (0.0)	0.73 (0.03–15.30)	1.000
Microbiology				
CSF culture ≥2 isolates	5 (9.8)	2 (22.2)	2.63 (0.43–16.26)	0.281
Gram-negative pathogen	29 (56.9)	7 (77.8)	2.65 (0.50–14.05)	0.293
Third-generation cephalosporin resistant GNB	16 (31.4)	5 (55.6)	2.73 (0.65–11.56)	0.255
Appropriate antimicrobial therapy				
"Initial" therapy[e]	22 (43.1)	6 (66.7)	2.64 (0.59–11.73)	0.281
Duration of therapy (d)	24±29	24±23	–	0.967

[a]Categorical data presented as n (%) of patient while continuous data presented as mean±standard deviation; [b]aneurysm (n=1), cerebrospinal fluid rhinorrhea (n=2), hydrocephalus (n=4), skull deformity (n=2); [c]only variables of p<0.05 and selected non-significant on univariate analysis are shown; [d]external ventricular drain or ventriculorperitoneal shunt (external lumbar cistern drain was not included); [e]given within 24 hours of presentation of meningitis. OR=Odds ratio; CI=confidential interval; CSF=cerebrospinal fluid; CRP=C-reactive protein; CVA=cerebrovascular accident; GNB=Gram-negative bacilli; GCS=Glasgow Come Scale.

Table 5. Multivariate analysis of risk factors for in-hospital mortality in nine deceased cases

Variables[a]	Module A		Module B		Module C	
	Adjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
GNB in CSF	1.39 (0.18–10.60)	0.753	–	–	–	–
Third-generation cephalosporin sensitive GNB in CSF[b]	–	–	0.02 (0.00–1.03)	0.052	–	–
Third-generation cephalosporin resistant GNB in CSF	–	–	–	–	33.65 (1.05–1,083.35)	0.047
Shock	0.67 (0.06–7.88)	0.747	0.81 (0.05–12.69)	0.878	1.66 (0.08–35.95)	0.748
Respiratory failure	6.86 (0.84–56.01)	0.072	19.36 (1.30–289.12)	0.032	30.33 (0.95–968.00)	0.053
Initial GCS score on presentation	1.00 (1.00–1.00)	0.172	1.37 (0.94–2.01)	0.104	1.19 (0.85–1.66)	0.307
Platelet count	1.24 (0.91–1.69)	0.129	1.00 (1.00–1.00)	0.027	1.00 (1.00–1.00)	0.083

[a]All variables included in the final multivariable model are shown; [b]third-generation cephalosporin sensitive GNB refer to GNB susceptible to ceftriaxone and ceftazidime. OR=Odds ratio; CI=confidential interval; CSF=cerebrospinal fluid; GCS=Glasgow Come Scale; GNB=Gram-negative bacilli.

which appeared much higher than that observed in previous studies (around 0.12:1 to 1.04:1).[1,3,14,15] One possible explanation for this higher ratio is the frequent aspiration of gastric contents with colonization of Gram-negative aerobes in head-injured patients,[16] or the broadly empirical use of vancomycin for post-surgical infections.[7]

Second, the finding of microbiologic distribution is not in accordance with the results of previous studies.[11,13,17,18] This study revealed the emergence of the uncommon CNS pathogens, *S. marcescens* and glucose non-fermenting GNB other than *Acinetobacter* spp. and *P. aeruginosa*. *S. marcescens* and *K. pneumoniae* were the two most common GNB in the post-neurosurgical meningitis, which accounted for 10.1% and 8.7%, respectively. In most of the published studies regarding Gram-negative bacillary meningitis, the common causative micro-organisms in post-neurosurgical meningitis were *Escherichia coli*, *K. pneumoniae*, and *P. aeruginosa*.[17,19] In Taiwan, *K. pneumoniae* has been a very common pathogen of acute bacterial meningitis and most cases were spontaneous and community-acquired infections.[20] *Klebsiella* meningitis has been frequently reported in patients with alcoholic liver disease and diabetes mellitus.[21,22] Although the incidence of *Klebsiella* meningitis decreased in this study, *K. pneumoniae* remained the commonly implicated pathogen.

S. marcescens, rather than *P. aeruginosa*, was the most common pathogen isolated from the CSF cultures in this study. *S. marcescens,* a rare pathogen in adult CNS infections, is recognized as a member of the *Enterobacteriaceae* and has been recovered from various sources.[23] It has been implicated in outbreaks of nosocomial infections in both neonates and adults.[24] Adult patients who have experienced head trauma or have undergone neurosurgery are at risk of developing *S. marcescens* CNS infection.[25] Compared with many other studies, we report an apparently larger number of *S. marcescens* meningitis episodes during a relatively short period of 2 years.

Third, the increasing number of third-generation cephalosporin-resistant GNB isolates challenges the existing therapeutic options for this serious CNS infection after neurosurgery. Third-generation cephalosporins have been widely used for the treatment of patients with

post-neurosurgical meningitis because these antibiotics penetrate well into the CSF after intravenous administration and this has resulted in dramatic decrease in meningitis-related mortality.[26] This study shows the spread of serious resistance to third-generation cephalosporins in nosocomial GNB throughout neurosurgical units. Before the start of treatment, GNB resistance to ceftriaxone and ceftazidime was 58.1% and 34.9%, respectively. Likewise, antimicrobial resistance has been reported in other studies,[16,17] but we report a quite large number of resistant strains in Taiwan. The reason for this high resistant rate to third-generation cephalosporins is probably attributable to the emergence of third-generation cephalosporin-resistant pathogens, e.g. *K. pneumoniae, E. cloacae* and glucose non-fermenting GNB. Univariate analysis showed that there was no statistically significant relationship between third-generation cephalosporin exposure (at least 72 hours) within 2 weeks before the onset of meningitis and third-generation cephalosporin resistance of GNB ($p=0.153$). Further research is needed to determine why these resistant strains are increasing.

Post-neurosurgical meningitis is still a high mortality disease (15.0%, 9/60 in this study). Many potential prognostic factors were analyzed, but only the presence of shock, respiratory failure, low GCS score at the onset of meningitis, and decreased platelet count were associated with the prognosis by univariate analysis. Although the presence of GNB in the CSF was not significantly related to death, the data reflect a strong trend towards in-hospital mortality (77.8 % *vs.* 56.9%; $p=0.293$). Subsequently, multivariate analysis showed that only the presence of third-generation cephalosporin resistant GNB in the CSF was independently associated with in-hospital mortality ($p=0.047$; Table 5, module C). This finding challenges the current concept regarding the choice of empiric antibiotic regimen for post-neurosurgical meningitis. Carbapenems have been recommended as the initial choice of empiric therapy for post-neurosurgical meningitis probably caused by Gram-negative bacteria.[10,17] Although we have investigated the impact of third-generation cephalosporin resistant GNB on in-hospital mortality, further research and constant epidemiologic trend analysis still needed to clarify this observation. Although this study is limited by low case numbers and a short study period, it is hoped that it can serve as the basis for further study.

In conclusion, Gram-negative pathogens, especially third-generation cephalosporin-resistant strains, have become increasingly common as the causative pathogens of CNS infection in post-neurosurgical patients. Prudent use of antibiotics requires that clinical decision-making takes into account both the risk to the individual patient if not covered appropriately for a certain pathogen, and the risks associated with overuse of antibiotics. Based on this study, empiric use of third-generation cephalosporins should be reassessed in patients with post-neurosurgical meningitis and it would be sensible to initiate further studies of other potentially effective agents such as carbapenem as the early empiric therapy. Although this preliminary study cannot conclude that the empiric use of carbapenem improves the survival of patients with post-neurosurgical meningitis, we suggest further investigations be carried out into this possibility.

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